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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,768	09/28/2001	Derek Van Der Kooy	Bereskin & Parr	6817

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,768	VAN DER KOOY ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February, 14 March, and 5 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17,20-22,25-27,29,30,33-38,41,42,47-49 and 51-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,20-22,25-27,29,30,33-38,41,42,47-49 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Papers filed 16 February 2006, 14 March 2006 and 5 April 2006 in response to the Non-Final Office Action mailed 10 August 2005. Claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42 and 47-49 were considered in the 10 August Office Action. Claims 1, 20, 33, 35, 37 and 47 were amended and claims 51-59 were added in the 20 May Paper. Claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42, 47-49 and 51-59 are pending and under consideration.

Response to Amendment, arguments and the Declarations under 37 CFR §1.132

Claim Rejections - 35 USC § 112

Claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42, 47-49 **stand rejected** and newly added claims 51-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mammalian primitive neural stem cell and a method of making and using a primitive neural stem cell wherein the primitive neural stem cell are produced from a culture of mammalian ES cells, does not reasonably provide enablement for a neural stem cell, method of making or method of using a neural stem cell wherein the cell is produced from the broad scope of any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This rejection is withdrawn to the extent that the Declarations of Derek van der Kooy evidence that the method disclosed in the application is capable of providing primitive neural stem cells from cultures of divergent mammalian species. However, the claims still encompass

primitive neural stem cells and methods of making primitive neural stem cells from all species of animal (e.g., all species of insect, amphibian, avian, reptile, etc.). Given the tremendous breadth of the claims and the unpredictable nature of the art, for the reasons set forth in the previous Office Action the skilled artisan would expect that developing the method such that one would be able to obtain a primitive neural stem cell from any species of animal would require undue trial and error experimentation. The showings of the declarations filed 14 March 2006 and 5 April 2006 are insufficient to overcome the rejection because they fail to evidence enablement commensurate with the scope of the presently claimed subject matter.

Applicant's arguments and the showings of the declaration have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking enablement for the full scope of what is claimed.

Claim Rejections - 35 USC § 102

Claims 25-27, 29, 30, 48 and 49 **stand rejected** and newly added claims 57-59 **are rejected** under 35 U.S.C. 102(b) as anticipated by Dinsmore *et al.* (1998) *Theriogenology* 49:145-151 for the reasons of record and set forth herein below in response to Applicant's arguments.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant contends that the Examiner has set forth an improper inherency rejection. Applicant cites *Ex parte Levy* wherein the Board

states, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."

Applicant contends that because Dinsmore et al. employed media containing serum for differentiating the ES cells and thus the cells were exposed to a myriad of different known and unknown factors, the cells of Dinsmore may never have contained primitive neural stem cells at any point. (Page 13 of the 16 February remarks.)

This argument has been fully considered but is not deemed persuasive. The Office Action (p. 8) cites *Ex parte Phillips* (BPAI 1993), *In re Best* (CCPA 1977) and *Ex parte Gray* (BPAI 1989) as standing for the principle that, because the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. The Office Action further cites *In re Fitzgerald* as finding that the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his or her claimed product.

In *Ex parte Phillips*, the Examiner concluded, based on the similar properties of the antigens recognized by the claimed monoclonal antibody and the monoclonal antibody of the prior art, that the claimed invention was anticipated by the art unless the Appellant could establish otherwise. The Board rejected the Appellant's arguments which were characterized as

establishing, at best, "that there *might* be a difference between the claimed subject matter and the hybridoma and monoclonal antibody disclosed by [the prior art]" the Board goes on to state, "There is no evidence of record which establishes that the respective antigens do, in fact, differ or the significance of such a difference. As set forth in *In re Best*, the Patent and Trademark Office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference in the first instance between the respective products, i.e., the claims are directed to new materials, and that such a difference would have been considered unexpected by one of ordinary skill in the art, i.e. the claimed subject matter, if new, is unobvious. This is appellants' burden. Rather than speculate about possible differences, appellants should have presented factual evidence which establishes that actual, unobvious differences exist between the respective materials." (*Phillips* at page 1303; emphasis added). By the same reasoning, Applicant's assertion in the instant case that "the cultures of Dinsmore et al. may never have contained primitive neural stem cells at any point" is not sufficient to establish that the claims novel and unobvious over Dinsmore et al.

Furthermore, the reasoning behind the inherency argument, as stated in the Office Action is not only that the specification discloses the claimed "primitive neural stem cell" as a previously unidentified stage in the neural lineage, which defines the transition between ES cell and neural stem cell. (Specification paragraph bridging pages 3-4.) As discussed in the Office Action, the specification also teaches in Example 8 that high density cultures plated in the absence of a feeder layer and the presence of serum (i.e., the conditions used in the method of Dinsmore et al.) contain $Nestin^+$, $SSEA\text{-}1^-$ cells having morphology that is consistent with $Nestin^+$ cells of the low density cultures. (See especially p. 39, ll. 15-30.) Given all of the

information presently of record, the skilled artisan would conclude, absent evidence to the contrary, that ES cell cultures treated as described in Dinsmore et al. would comprise primitive neural stem cells.

It is also noted that there is nothing of record to support Applicant's postulate that there is some alternative pathway from ES cell to neural stem cell that does not proceed through a "primitive neural stem cell". That is, there is nothing of record to suggest that there are multiple pathways leading from ES cell to neural stem cell, only some of which involve a "primitive neural stem cell" as recited in the instant claims. In fact, it would appear from the specification as a whole that the claims cover any transitional state between ES cell and definitive neural stem cell and does not distinguish between possible alternative transitional states. Given that Dinsmore et al. teaches culturing ES cells under conditions that are demonstrated in the instant Example 8 to comprise some cells having characteristics of primitive neural stem cells, and Dinsmore et al. teaches differentiation of ES cells to neuronal cells, the skilled artisan would expect, absent evidence to the contrary, that primitive neural stem cells are a component of the cultures of Dinsmore et al.

In the first full paragraph on page 14 or the remarks, Applicant contends that a transient presence of primitive neural stem cells in a culture does not satisfy the requirements of being "isolated". However, it is unclear precisely what Applicant views as the requirements of being "isolated". The specification does not set forth a limiting definition of "isolated" and there is nothing of record to suggest that primitive neural stem cells present in a culture such as that described in the instant Example 8 and in the method of Dinsmore et al. are not within the broadest reasonable interpretation of the term isolated. The cells are clearly not a part of an

organism and, as suggested by Example 8, primitive neural stem cells in high-density cultures tend to arise in regions of relatively low cell density (i.e., relatively isolated regions). Therefore, absent evidence to the contrary, the cells of Dinsmore et al. are considered "isolated" according to the broadest reasonable construction of the claim limitation.

In the second full paragraph on page 14, Applicant notes that Dinsmore et al. teaches culturing ES cells according to standard methods used in the field and differentiation of the cells to neuronal cells using a specialized media. Applicant contends that Dinsmore et al. makes no mention of a neural stem or progenitor cell characteristics and the presence of uncharacterized molecules in the specialized medium were entirely distinct from the media employed in the instant application and would have affected the ES cell differentiation differently from the conditions used in the instant application. In the first and second paragraphs on page 15 of the remarks, Applicant contends that the population of neuronal cells that are ultimately produced in the method of Dinsmore et al. are not neural stem or progenitor cells and that the absence of glial-specific markers in the cells of Dinsmore et al. clearly indicate that they have isolated differentiated neurons and not multipotent primitive neural stem cells.

These arguments have been fully considered but are not deemed persuasive. It is first noted that anticipation under 35 USC §102 does not require that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). See also MPEP 2112. As discussed herein above, the specification also teaches in Example 8 that high density cultures plated in the absence of a feeder layer and the presence of serum (i.e., the conditions used in the

method of Dinsmore et al.) contain Nestin$^+$, SSEA-1$^-$ cells having morphology that is consistent with Nestin$^+$ cells of the low density cultures. (See especially p. 39, ll. 15-30.) Given all of the information presently of record, the skilled artisan would conclude, absent evidence to the contrary, that ES cell cultures treated as described in Dinsmore et al. would comprise primitive neural stem cells. There is no requirement under 35 USC §102 that Dinsmore et al. be aware of the presence of the primitive neural stem cells.

Furthermore, Dinsmore et al. teaches the *in vitro* differentiation of ES cells to neuronal cells which, absent evidence to the contrary, would involve a primitive neural stem cell intermediate. The specification discloses the claimed "primitive neural stem cell" as a previously unidentified stage in the neural lineage, which defines the transition between ES cell and neural stem cell. (Id.) As discussed above, there is no evidence to suggest that there are alternative pathways leading from ES cell to neuronal cell that do not involve a primitive neural stem cell intermediate. Furthermore, there is no limiting definition of a "primitive neural stem cell" in the specification that would suggest that some transitional states between ES cell and definitive neural stem cells are included while other transitional states between ES cell and definitive neural stem cell are excluded from the scope of the claimed invention. Given that the method of Dinsmore et al. starts with a population of ES cells and, as Applicant acknowledges, ends with a population of neuronal cells it is reasonable to conclude that the process of differentiation involved an intermediate primitive neural stem cell. Therefore, absent some evidence to the contrary, the claimed primitive neural stem cell is anticipated by the art.

Finally, Applicant contends that the cell aggregates disclosed in Dinsmore et al. do not meet the limitation of a "sphere colony" because the instant specification indicate that the

spheres derived from the ES cells in the application are a result of the clonal proliferation of a single cell. In support of this contention, Applicant cites teachings at page 15, lines 4-10 and page 30, lines 7-9.

This argument has been fully considered but is not deemed persuasive. Claim 49 is directed to "[a]n isolated sphere colony comprising a primitive neural stem cell". The teachings cited by Applicant state that single cells clonally proliferate to form spheres (p. 15) and "sphere colonies generated from neural cells are specified to primarily neural identity and are composed of both neuronal and glial lineages" (p. 30). The cited passages appear to describe the properties of sphere colonies derived from the proliferation of ES cells and neuronal cells. They do not, however, provide a limiting definition of a "sphere colony". In other words, although the passages describe species of sphere colony, there is nothing in the passages cited or the specification as a whole to indicate that the limitation "sphere colony" is limited to only these species. Therefore, the cell aggregates comprised in the cultures of Dinsmore et al. are within the broadest reasonable interpretation of what is presently claimed.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §102(b) as anticipated by the art.

With respect to newly added claims 57-59, which recite that the primitive neural stem cell expresses one of various markers including nestin, in view of the evidence that the cultures of Dinsmore et al. comprise primitive neural stem cells and the evidence provided to indicate that primitive neural stem cells express the markers recited in the claims, the skilled artisan would conclude, absent evidence to the contrary, that the cells of Dinsmore et al. express the recited

markers. Therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by Dinsmore et al. for the reasons set forth in the previous Office Action and herein above.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 20-22, 29, 33-38, 41, 42, 47 and 56 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for differentiating one or more pluripotent mammalian ES cells to primitive neural stem cells, wherein the method comprises culturing ES cells at low cell density in serum-free and feeder-layer free medium in the presence of LIF, does not reasonably provide enablement for the method wherein the cells are cultured in serum-free and feeder layer-free medium in the absence of LIF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method for differentiating one or more pluripotent embryonic stem cells to primitive neural stem cells, wherein the method comprises culturing ES cells at low cell density (defined in the specification at p. 14, ll. 17-19 as referring "to a cell culture density at which cell proliferation can occur with minimal and preferably no aggregation of ES cells or EB formation") in serum-free and feeder-layer free medium. The previously examined claims also recited that the culturing is carried out the presence of LIF. In the 16 February Paper, the claims were amended to recite that the presence of LIF in the serum free and feeder-layer free media is "optional". Therefore, the claims now encompass a method of obtaining primitive neural stem cells from ES cells in serum free and feeder-layer free media wherein the media does not comprise LIF.

State of the prior art and level of predictability in the art: The prior art provides no guidance with regard to obtaining primitive neural stem cells by a process involving culturing ES cells at a low cell density in serum-free and feeder layer-free medium. However, Tropepe et al. (2001) *Neuron* 30:65-78 clearly demonstrates that mouse ES cells plated at low density in serum free medium in the absence of a feeder layer do not generate colonies comprising primitive neural stem cells, evidencing that primitive neural stem cells capable of self-renewal are not produced in serum-free and feeder layer-free medium the absence of LIF (see especially Figure 1A and the caption thereto).

Amount of direction provided by the inventor and existence of working examples: Although the instant application provides prophetic teachings wherein neural cells are obtained

from ES cells by culturing cells in serum free media, wherein the teachings do not require that LIF is present in the culture medium (see, e.g., page 4, 3rd full ¶), the instant specification, like Tropepe et al., teaches that LIF is required in order to obtain primitive neural stem cells from low-density cultures of ES cells in serum-free and feeder-layer free medium. The specification teaches:

"[Primitive neural stem cells] can be isolated by their ability to form neurospheres in the presence of LIF (and not FGF2)." (P. 15, ll. 17-18.);

"The novel primitive neural stem cells of the invention (the LIF dependent cells) have a much greater degree of pluripotential fates than do definitive neural stem cells..." (P. 15, ll. 21-21-23.);

"When ES cells were cultured at relatively low densities in the presence of either EGF or FGF2 or in the absence of exogenous growth factors no cell colonies were generated (Figure 1A). In contrast, in the presence of exogenous leukemia inhibitory factor (LIF), which is normally used to maintain ES cells in an undifferentiated state [], floating sphere-like colonies were generated after 7 days in vitro...exogenous EGF and FGF2 were neither necessary nor sufficient for colony formation in primary cell cultures. Furthermore, CNTF, another member of the cytokine family of signaling molecules to which LIF belongs [], was unable to substitute as a colony-promoting factor (data not shown), suggesting that the effects of LIF are specific." (P. 26, ll. 3-9; emphasis added, citations omitted);

"LIF and FGF are critical for ES-derived neural stem cell colony formation and subsequent subcloning (stem cell self-renewal). This is in contrast to neural stem cells isolated

from embryonic or adult tissues, where either exogenous FGF or EGF is sufficient for colony formation and subcloning." (P. 47, ll. 2-6.);

"[G]rowth factor requirements may be sequentially modified from a primitive neural stem cell stage (LIF- and FGF-dependent) to an early embryonic neural stem cell stage (only-FGF dependent), and finally to a relatively mature neural stem cell stage where both FGF- and EGF-dependent subpopulations co-exist..." (P. 47, ll. 18-22.);

"[F]urther studies will be required to determine more precisely the factors that mediate the transition from a LIF- and FGF-dependent primitive neural stem cell to a definitive FGF-dependent neural stem cell that can give rise to EGF dependent neural stem cells at later embryonic ages." (P. 47, ll. 29-33.)

Thus, the specification teaches that colonies containing primitive neural stem cells could not be obtained from cultures of mouse ES cells in serum-free and feeder-layer free medium in the absence of LIF and closely related molecules such as CNTF could not substitute for LIF. Furthermore, the specification teaches that neural stem cells that are no longer LIF-dependent are not "primitive neural stem cells", but are instead more definitively differentiated neural stem cell populations.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill in the art would not be able to practice the full scope of the claimed method of obtaining a "primitive neural stem cell" by culturing ES cells in serum-free and feeder-layer free medium. Given the teachings of Tropepe et al. and the teachings of the specification, which demonstrate that LIF is required to obtain colonies comprising primitive neural stem cells from ES cells under the

conditions recited in the instant claims, the skilled artisan would not know how to obtain a primitive neural stem cell according to the method without the inclusion of LIF in the culture medium. In particular, the specification teaches that even closely related agents such as CNTF cannot substitute for LIF in serum-free and feeder layer-free cultures of ES cells plated at low density. Therefore, in order to practice the claimed method wherein the culture medium does not comprise LIF, the skilled artisan would be required to identify culture conditions that could substitute for LIF in providing primitive neural stem cells from ES cells cultured at low-density in serum-free and feeder-layer free medium. Therefore, the application fails to enable the claimed invention beyond the scope of the method practiced wherein the medium contains LIF.

Response to the Declaration filed 5 April 2006

In the 14 March Declaration of Derek van der Kooy, Declarant states that the purpose of the declaration is to provide factual evidence that primitive neural stem cells can be generated from embryonic stem cells in the absence of LIF. (¶3.) The Declaration demonstrates derivation of primary neurospheres from human ES cells grown at 10 cells/μl. Specifically, human ES cells were cultured in medium comprising EGF, FGF, heparin and B27 with or without LIF. The data provided show that neurospheres were generated, albeit at a lower frequency, in the cultures that did not comprise LIF. Declarant states, "This data shows that LIF is optional for production of human primitive neural stem cells." (¶7.)

The showings of the Declaration have been fully considered but are not deemed persuasive in view of the record as a whole. First, the declaration contains no evidence to show that the neurospheres obtained from human ES cells comprise "primitive neural stem cells" and

are not comprised solely of more definitively differentiated cells. Such evidence is critical because the specification clearly teaches that neural stem cells that do not require LIF are developmentally distinct from "primitive neural stem cells". (See the passages at p. 15, ll. 21-23; p. 47, ll. 2-6, p. 47, ll. 18-22; and p. 47, ll. 29-33 cited herein above.) Furthermore, even if the Declaration had demonstrated that the neurospheres derived from human ES cells in the absence of LIF comprise "primitive neural stem cells" the teachings of the specification clearly evidence that obtaining primitive neural stem cells from ES cells plated at low density in serum-free and feeder-layer free medium in the absence of LIF is species specific and unpredictable. Therefore, the showings of the declaration, considered in view of the record as a whole, would not support enablement for the full scope of what is presently claimed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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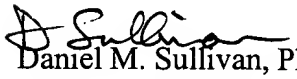

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Art Unit 1636